Personal Interview

Applicants express their thanks to the Examiner for the opportunity to discuss the outstanding rejections during a personal interview on July 25, 2003. The interview specifically included an analysis of the Pitner et al. reference, in comparison with the screening assay claimed in the present application. The Examiner informed Applicants' representatives that significant amendments would likely not be considered following a final rejection. Applicants have offered to file a Request for Continued Examination, accompanied by detailed written argumentation, which is done by the current Preliminary Amendment.

Turning to the Office Action, prior to the entry of the present Preliminary Amendment, Claims 40, 41, 43, 45-51, 59 and 60 were pending in this application. Claims 59 and 60 have been withdrawn from consideration as a result of an election of species requirement. Claims 40, 41, 43 and 45-51 have been rejected on various grounds.

Election/Restriction

With regards to the election of species requirement, the Examiner notes that Applicants' elected species was found in the prior art, and cites MPEP § 803.02 to explain that in this situation, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. Applicants believe that from the analysis of the cited prior art it will be apparent that the elected species in not anticipated or rendered obvious by prior art. Accordingly, under the same section, claims 59 and 60 should be reunited with the rest of the claims pending, including newly added claim 64, and examined in the present application for their full scope.

Claim Rejections - 35 U.S.C. §102

Claims 40-41, 43 and 45-46 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Pitner et al. (U.S. Patent No. 5,367,058).

The rejection is respectfully traversed.

Pitner et al. concerns the modification of antibodies with affinity labeling reagents. The antibodies are modified near to their antigen binding site, e.g. by the addition of a thiol group, so that a covalent group can be formed between the antibody and an antigen binding to the antibody.

This approach is stated to increase the affinity of the antibody for its known antigen, as compared to the affinity of a corresponding unmodified antibody to the same known antigen.

Pitner et al. fails to disclose all elements of claim 40 and thus does not anticipate the invention as claimed in claim 40.

In particular, claim 40 includes the following elements:

a) obtaining a target protein comprising a -SH group, masked -SH group, or activated -SH group;

b) combining said target protein with a library simultaneously containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond, and wherein said ligand candidates each are less than about 2000 daltons in size, under disulfide-exchange conditions, in the presence of a reducing agent, wherein at least one ligand candidate binds to the target protein and forms a disulfide bond with the target protein to yield a target protein-ligand conjugate; and

c) determining the identity of the non-oligomeric ligand present in said target protein-ligand conjugate.

Pitner et al. does not teach element b) of claim 40, since it involves reacting a single antibody with a single antigen known for that antibody, and does not teach the screening of a library of ligand candidates with a target protein. Indeed, Pitner et al. does not teach any reaction between a target protein and a ligand candidate, since the disclosed method involves modifying a known antigen, i.e. the ligand is already known. In addition, Pitner et al. does not teach element b) of the invention claimed in claim 40, since the reaction of the antibody and its known antigen is not performed under disulfide exchange conditions, in the presence of a reducing agent. Although Pitner et al. teaches a process in which a reducing agent (DTT) is used, the reducing agent is removed prior to reacting the chemically modified (affinity labeled) antibody with its antigen. Therefore, the latter reaction is not performed under disulfide exchange conditions, in the presence of a reducing agent.

Pitner et al. fails to teach element c) of claim 40, since it does not disclose a step of determining the identity of a ligand present in a target protein-ligand conjugate. Such

identification step is not necessary, since the ligand (antigen) present in the antibody-antigen complex formed is known.

Indeed, one skilled in the art will appreciate that the method of Pitner at et. and the claimed invention are very different. The present invention concerns a screening assay to identifies a ligand covalently bound to a target protein via a chemical tether, from among a library of ligand candidates. This method is quite different from Pitner's interest in preparing and testing antibodies to identify those which display an increased affinity for a known antigen.

Since claim 40 is not anticipated, nor are the claims dependent thereon. Accordingly, the present rejection should be withdrawn.

Claim Rejections - 35 U.S.C. §103

Claims 40-41, 43 and 45-51 were rejected as allegedly obvious over Pitner et al. and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology, New York: Academic Press. 1996, pages 119-126).

Pitner et al. was applied as in the previous rejection under 35 U.S.C. §102. According to the rejection, "Pitner et al. teaches all the limitations sated in the 35 U.S.C. 102(b) rejection above . . . , which anticipates claims 40-41, 43 and 45-46 and, consequently, also renders obvious claims 40-41, 43 and 45-46." As discussed above, Pitner et al. does not teach all limitations of claim 40, or any of the claims dependent thereon, therefore, in order to establish a *prima facie* case of obviousness of the invention claimed in claims 40-41, 43 and 45-46 over Pitner et al. alone, the Examiner should have performed a proper legal analysis of obviousness determination. Although such analysis has not been performed, and therefore the burden to show non-obviousness of the claimed invention has not shifted to Applicants, in order to expedite prosecution applications submit the following arguments.

Although in Sibia Neurosciences, Inc. vs. Cadus Pharmaceutical Corporation, 225 F.3d 1349 (CAFC, 2000) the Federal Circuit found that a single prior art reference can render a patent claim obvious, it held that there must be a showing of a suggestion or motivation to modify the teachings of the reference to arrive at the claimed invention, in order to support the obviousness conclusion. The suggestion or motivation can be derived from the prior art reference itself,

knowledge of one of ordinary skill in the art or from the nature of the problem to be solved.

In the present case, such motivation does not exist. Since the objective of Pitner et al. was the testing of modified antibodies ("target proteins") for their binding affinity to their known antigens ("ligands"), reading this disclosure, and also in view of general knowledge in the art, one would not have been motivated to screen a library of ligand candidates for their binding ability to a given target protein. Similarly, in view of the teaching of Pitner et al. of the removal of the reducing agent before performing the reaction of the modified antibody with its antigen, one would not have been motivated to perform a screening assay where two binding partners are reacted under disulfide exchange conditions, in the presence of a reducing agent. Finally, based on the teaching of Pitner et al. and general knowledge in the art, one of ordinary skill would not have been motivated to determine the identity of the ligand participating in a target protein-ligand conjugate, since Pitner et al.'s teaching is specific to the reaction of a derivatized antibody with an antigen, the identity of which is known. Nor can the motivation be derived from the nature of the problem to be solved, since Pitner et al. and the present invention address significantly different problems. The problem to be solved in Pitner et al. is the increase of antibody affinity for the antigen to which the antibody binds. In contrast, the problem to be solved in the present invention is the identification of a ligand for a target protein from among members of a library of ligands. Accordingly Pitner et al. does not make obvious claims 40-41, 43 and 45-46.

Claims 47, and 48-51 were rejected as "obvious" over Pitner et al. in view of Siuzdak. Siuzdak was cited for its teaching of the use of electrospray mass spectrometry to study antibody-antigen interactions, including fragmentation techniques.

Claim 51 has been canceled. Without addressing the Examiner's analysis of Siuzdak in detail, Applicants submit that since Pitner et al. does not make obvious the claims on which claims 47 and 48-50 depend, these dependent claims are unobvious for the same reason.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1C2). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 2, 2003

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10/2/03 9:28 AM (39750.0002)